

**REMARKS**

Applicants have amended claims 1 and 15 to clarify the subject matter. Support for the amendment can be found throughout the specification (*e.g.*, page 2, lines 15-26; page 8, lines 9-22; Figures 1-4). No new matter has been added.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Applicants note that the Examiner has withdrawn the rejections under 35 U.S.C. § 102(e) in view of Applicants' Response filed on May 23, 2005.

**Rejection of Claims 1-5, 8, 15-20, and 37-40 under 35 U.S.C. § 112, Second Paragraph**

Claims 1-5, 8, 15-20, and 37-40 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite due to their recitation of Genbank Accession numbers. Specifically, the Examiner asserts that "Genbank Accession numbers are not stable and can be changed at any time." See Office Action, page 2, lines 12-13.

Applicants respectfully traverse the rejection and submit that reference to a GenBank Accession number does not render the claims indefinite. A person of ordinary skill in the art would be able to determine the nucleotide sequence of a gene by reference to its GenBank Accession number. Further, while a GenBank Accession number can be revised, a person of ordinary skill in the art would be to identify any revisions made to a sequence over time. Applicants enclose herewith as **Exhibit A** a print-out from the National Center for Biotechnology Information ("NCBI") website with respect to sequences revisions. The NCBI printout clearly indicates that a person reviewing the records for a particular GenBank Accession number would be able to determine whether a particular sequence has been revised and would be able to access previous versions of the sequence, *e.g.*, the version of the sequence in the database at the filing date of the subject application.

Further, a search of the United States Patent and Trademarks Office ("USPTO") granted patents database reveals that the USPTO has granted patents containing claims which

recite sequences by references to their GenBank Accession Numbers.<sup>1</sup> Thus, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Rejection of Claims 1-5, 8, 15-20, and 39-40 under 35 U.S.C. § 102(a)

Claims 1-5, 8, 15-20, and 39-40 are rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Alizadeh *et al.* (Nature (February 2000) 403:503-511), referred to herein as Alizadeh *et al.* (2000). Applicants respectfully traverse this rejection.

The standard for anticipation of a claim is clearly outlined in MPEP 2131, and this standard is further supported by the Courts. “A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1978). Applicants contend that Alizadeh *et al.* (2000) do not satisfy this criterion for anticipating the presently claimed invention.

Applicants have amended claims 1 and 15 for greater clarity. The amendments are fully supported by the specification (see, *e.g.*, page 2, lines 15-26; page 8, lines 9-22; Figures 1-4). Applicants submit that the pending claims as amended are novel over Alizadeh *et al.* (2000).

Claim 1 as amended is directed to a method of classifying a lymphoma sample according to predicted treatment outcome comprising determining a gene expression profile of gene expression products from at least two informative genes having GenBank Accession Nos. L20971 and M18255, wherein the gene expression products are isolated from one or more cells in the sample, and wherein the gene expression profile of the two informative genes having GenBank Accession Nos. L20971 and M18255 is correlated with a treatment outcome, thereby classifying the sample with respect to treatment outcome.

Claim 15 as amended is directed to a method of classifying a sample according to lymphoma type comprising determining a gene expression profile of gene expression

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<sup>1</sup> The query used was: “GenBank Accession Number” or “GenBank Accession No.” in claims. This search resulted in 23 hits. Among the relevant hits were: U.S. Patent Nos. 6,943,006, 6,890,572, 6,77,0742, and others.  
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products from at least two informative genes having GenBank Accession Nos. L17131 and U29680, wherein the gene expression products are isolated from one or more cells in the sample, wherein the gene expression profile of the two informative genes having GenBank Accession Nos. L17131 and U29680 is correlated with a lymphoma type, thereby classifying the sample with respect to lymphoma type.

Specifically, the Examiner asserts that “Alizadeh teaches the use of four different sequences on the microarray, one of which is identical to the elected sequences and the other three of which would hybridize specifically under the hybridization conditions used to the elected genes. Thus, Alizadeh expressly teaches detection of the four elected genes on the Lymphochip microarray.” See Office Action, page 12, lines 19-23.

Applicants respectfully disagree. Although Alizadeh *et al.* (2000) utilized the Lymphochip microarray comprising probes for the four elected genes (*i.e.*, GenBank Accession Nos. L20971, M18255, L17131, and U29680) and detected these four genes on the microarray, Alizadeh *et al.* (2000) do not disclose that the gene expression profile of the two informative genes (represented by GenBank Accession Nos. L20971 and M18255) is correlated with a treatment outcome as recited in amended claim 1. Nor do Alizadeh *et al.* (2000) disclose that the gene expression profile of the two informative genes (represented by GenBank Accession Nos. L17131 and U29680) is correlated with a lymphoma type as recited in amended claim 15. As a result, Alizadeh *et al.* (2000) fail to teach the method of classifying a lymphoma sample according to predicted treatment outcome as recited in claim 1 and the method of classifying a sample according to lymphoma type as recited in claim 15.

Since Alizadeh *et al.* (2000) do not teach or suggest a correlation of the four genes (*i.e.*, GenBank Accession Nos. L20971, M18255, L17131, and U29680) with a treatment outcome or a lymphoma type, Alizadeh *et al.* (2000) fail to meet the limitations of independent claim 1 or 15, and thus fail to anticipate the claimed subject matter. For the same reasons, Applicants submit that all claims depending from claims 1 or 15 are not anticipated by Alizadeh *et al.* (2000). Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(a) are respectfully requested.

Rejection of Claims 1-5, 8, 15-20, and 39-40 under 35 U.S.C. § 102(b)

Claims 1-5, 8, 15-20, and 39-40 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Alizadeh *et al.* (Cold Spring Harbor Symposium Quantitative Biology (June 1999) 64:71-78), referred to herein as Alizadeh *et al.* (1999).

Applicants respectfully traverse this rejection and believe that the pending claims as amended are novel over Alizadeh *et al.* (1999).

Like Alizadeh *et al.* (2000), Alizadeh *et al.* (1999) merely utilized the Lymphochip microarray comprising probes for the four elected genes (*i.e.*, GenBank Accession Nos. L20971, M18255, L17131, and U29680) and detected these four genes on the microarray. However, Alizadeh *et al.* (1999) do not disclose that the gene expression profile of the two informative genes (represented by GenBank Accession Nos. L20971 and M18255) is correlated with a treatment outcome as recited in amended claim 1. Nor do Alizadeh *et al.* (1999) disclose that the gene expression profile of the two informative genes (represented by GenBank Accession Nos. L17131 and U29680) is correlated with a lymphoma type as recited in amended claim 15. As a result, Alizadeh *et al.* (1999) fail to teach the method of classifying a lymphoma sample according to predicted treatment outcome as recited in claim 1 and the method of classifying a sample according to lymphoma type as recited in claim 15.

Since Alizadeh *et al.* (1999) do not teach or suggest a correlation of the four genes (*i.e.*, GenBank Accession Nos. L20971, M18255, L17131, and U29680) with a treatment outcome or a lymphoma type, Alizadeh *et al.* (1999) fail to meet the limitations of independent claim 1 or 15, and thus fail to anticipate the claimed subject matter. For the same reasons, Applicants submit that all claims depending from claims 1 or 15 are not anticipated by Alizadeh *et al.* (1999). Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) are respectfully requested.

**CONCLUSION**

In view of the foregoing amendments and remarks, the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Applicants believe that no further fee is due with this response beyond those transmitted herewith. However, if a fee is due, please charge our **Deposit Account No. 18-1945, under Order No. WIBL-P01-579.**

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Respectfully submitted,

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## Sequence Revision History Page Offers New Comparison Functions

Changes in records from the Entrez Nucleotide and Protein databases can now be visualized using the Sequence Revision History tool at:

[www.ncbi.nlm.nih.gov/entrez/sutils/girevhist.cgi](http://www.ncbi.nlm.nih.gov/entrez/sutils/girevhist.cgi)

To retrieve the history of a record, one can enter the accession number, the GI number, or the FASTA-style SeqID of that record into the query box at the top of the page.

Figure 1 shows the revision history table for the nucleotide sequence AF123456. The table displays the dates of changes made to the record since it was first released. The first two columns contain, respectively, the GI numbers and the version numbers of the sequence, which are only changed if the sequence data itself has been modified.

Updates to any record may include changes to the sequence, publication information, or annotations made by the authors. In this case, the sequence data has been modified once. The "Update Date", identical to the "Modification Date" seen on the Entrez Limits page, is the date that appears in the upper right hand corner in the flat file view of Entrez records. The "Status" column indicates the most recently-updated version of the record, the "Live" record, that is retrievable from Entrez; the older versions have a status of "Dead". The date the record was first seen at NCBI is given at the bottom of the table.

### Revision history for AF123456

GI	Version	Update Date	Status	I	II
6633795	2	<u>Jul 25 2000 8:09</u>	Live	<input checked="" type="radio"/>	<input type="radio"/>
6633795	2	<u>Jan 28 2000 5:18</u>	Dead	<input type="radio"/>	<input checked="" type="radio"/>
6633795	2	<u>Dec 23 1999 2:25</u>	Dead	<input type="radio"/>	<input checked="" type="radio"/>
4454562	1	<u>Mar 23 1999 1:24</u>	Dead	<input type="radio"/>	<input checked="" type="radio"/>
4454562	1	<u>Mar 20 1999 12:06</u>	Dead	<input type="radio"/>	<input checked="" type="radio"/>

Accession AF123456 was first seen at NCBI on Mar 20 1999 12:06

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**Figure 1.** The Sequence Revision History table for AF123456. The last two versions of the record have been selected for comparison.

The last two columns are labeled I and II, respectively, and are used to select the two versions of the record to compare. One can view the differences in several display formats, including GenBank/GenPept flat file, XML, and ASN.1. The differences between the records are highlighted in color, as shown in Figure 2. The "GenBank diff"

format lists the differences in the manner of the UNIX “diff” command, without highlighting. The FASTA and BLAST formats can be used to pinpoint differences in the sequence data.—VP

Show difference in		GenBank/GenPept	format	Show	Update Date
GI	6633795	GenBank/GenPept			Jul 25 2000 8:09
	6633795	GenBank Diff			Jan 28 2000 5:18
		ASN.1			
		FASTA			
		XML			
		BLAST			
LOCUS	AF1234	1510 bp	mRNA	linear	VRT 28-JUL-2000
LOCUS	AF123456	1510 bp	mRNA	linear	VRT 28-JAN-2000
DEFINITION	Gallus gallus doublesex and mob-3 related transcription factor 1 (DHRT1) mRNA, partial cds.				
ACCESSION	AF123456				
VERSION	AF123456.2 GI:6633795				
KEYWORDS	.				
SOURCE	Gallus gallus (chicken)				
ORGANISM	Gallus gallus				
	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Archosauria; Aves; Neognathae; Galliformes; Phasianidae; Phasianinae; Gallus.				

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**Figure 2.** GenBank display of the differences between two versions of AF123456. Sections of the record in which there are differences are shown for each version and highlighted.

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